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A COMPREHENSIVE REVIEW ON PRODRUGS OF BIOACTIVE OF NATURAL ORIGIN

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ABSTRACT: Prodrugs are bio-reversible, inactive drug by products that can convert into a parent drug inside the body. Around 10% of the medications accepted globally can be categorized as prodrugs. Prodrugs are designed to enhance the site-selective delivery of an active drug by modifying the physicochemical and pharmacokinetic properties of pharmacologically potent compounds. Prodrugs are changed and form active drugs inside the body through enzymatic or non-enzymatic reactions. This article describes the potent secondary metabolites from natural sources that are amenable to prodrug design. A fair number of them have issues of bioavailability and metabolism, resulting in less efficacy, and a prodrug strategy is required to improve their efficacy. This has come into the spotlight recently by achieving encouraging results in most cases. Many phytochemicals are not preferred due to their low solubility, decreased bioavailability, and adverse effects, but these problems can be overcome with the formation of prodrugs of such compounds. Several techniques can be used to synthesize these prodrugs, including biotransformation, electrophilic substitution, esterification, biomodulation, covalent conjugation, and complex formation. A detailed study of the problem encountered by the bioactive of natural origin, the process of formation of their prodrugs and the advancements produced due to the generation of such prodrugs are discussed in this review & takes the focus on the foremost utilization of the prodrug approach, comprising the capability to enhance oral absorption & aqueous solubility, enhance lipophilicity, increase active transport, and also attain site-selective application.

INTRODUCTION: A prodrug is a chemically modified form of a pharmacologically active molecule that remains inactive or less active until it transforms within the body. This conversion may occur through enzymatic or non-enzymatic pathways, releasing the active drug at the site of action¹.

A prodrug typically consists of two components: the parent drug and a moiety. While the moiety itself does not exhibit therapeutic activity, it is strategically selected to improve critical drug properties such as solubility, absorption, stability, or targeting ability¹⁻⁴.

The major purpose of prodrug design is to overcome shortcomings of bioactive compounds, such as poor solubility in water or lipids, limited tissue selectivity, unfavorable taste, local irritation, rapid metabolism, or systemic toxicity. By modifying such compounds into prodrugs, their pharmacokinetic and pharmacodynamic profiles

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absorption, distribution, metabolism, excretion (ADME) can be enhanced, leading to safer and more effective therapies. Plant-derived secondary metabolites are of particular interest because they provide a wide range of bioactive molecules with diverse chemical scaffolds.

However, many of these phytochemicals suffer from inadequate solubility, poor permeability, instability, and rapid metabolism, limiting their therapeutic potential. Prodrug strategies, including polymer conjugation and nanodrug formation, have been investigated to improve these limitations, especially in the field of cancer therapy⁵.

This review highlights the design, synthesis, and applications of prodrugs derived from natural compounds, emphasizing examples with anticancer, antimicrobial, and antioxidant potential.

Categories of Prodrugs: Prodrugs can be classified according to the mechanism by which they are activated inside the body⁶⁻¹².

Bioprecursor Prodrugs: These do not carry an additional promoiety. Instead, they rely on metabolic transformation by enzymes to generate the active compound.

Carrier-Linked Prodrugs: Here, the drug is attached to a carrier group (commonly esters, phosphates, or amides) that enhances solubility or permeability. The carrier is cleaved enzymatically or chemically after administration to release the active drug.

Schiff Base Prodrugs: These involve imine or enamine linkages with primary amines. They increase lipophilicity and reduce ionization, improving membrane transport. They are generally stable but can hydrolyze *in-vivo* to release the parent amine.

N-Mannich Base Prodrugs: Created by derivatizing amides or amines with a Mannich base, these derivatives improve aqueous solubility and lipophilicity. They are stable under certain conditions but release the parent drug *in-vivo* through hydrolysis.

Formation of Trisindolines from Isatin: Isatin, also called tribulin, is an indole-based molecule

known for antitumor, antiviral, anti-HIV, and antitubercular activities¹³. However, due to its limited potency, researchers have designed trisindolines, which are condensation products of isatin with indoles. These compounds exhibit a broad range of bioactivities, including anticancer, antimicrobial, antifungal, and antioxidant effects.

The synthesis of trisindolines usually involves acid-catalyzed electrophilic substitution reactions between indole and isatin. The reaction mechanism proceeds *via* an intermediate (3-hydroxy-3-indolyl-2-indolone) which, upon further reaction with indole, yields 3,3-di(3-indolyl)-2-indolone^{14, 15}.

Different catalysts are used for these reactions:

- Mineral acids such as sulphuric¹⁶, phosphoric¹⁷, and tungstic acids¹⁸.
- Organic acids, including p-toluenesulfonic acid, acetic acid, and sulfamic acid^{19, 20}.
- Halogen-based catalysts, e.g., iodine²¹ or N-bromosuccinimide²².
- Metal-based catalysts, such as aluminium sulfate or ceric ammonium nitrate, are cost-effective but require careful handling²³.

Problems Faced During the Administration of Drugs, Along with Their Solutions: Many drugs fail during formulation because of poor solubility, inadequate stability, or undesirable sensory properties. Prodrug design offers an efficient solution to such limitations²⁴.

Poor Solubility: Buparvaquone suffers from poor water solubility. By converting it into phosphate ester derivatives, solubility and skin permeability were improved, enhancing its oral and topical bioavailability **Fig. 1**²⁵⁻²⁸.

Paclitaxel is another poorly soluble drug. The prodrug isotaxel, created via O,N-acyl migration, displays improved solubility and bioavailability **Fig. 2**^{24, 25, 29}.

Dapsone derivatives linked with amino acids showed improved aqueous solubility while retaining antimicrobial activity¹⁹.

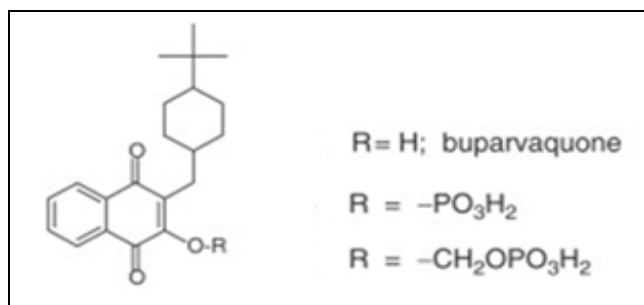


FIG. 1: BUPARVAQUONE AND ITS PRODRUGS

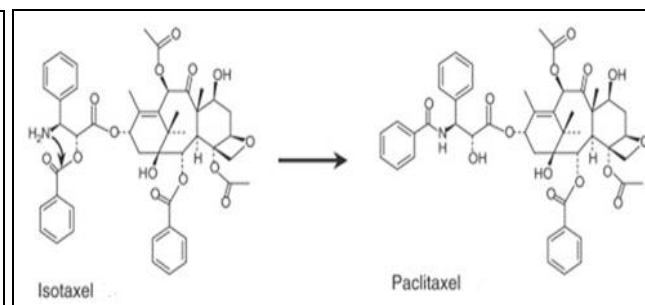


FIG. 2: PACLITAXEL AND ITS PRODRUGS ISOTAXEL

Unpleasant Taste: Erythromycin-A has a strong bitter taste, leading to poor compliance in children. Its tasteless prodrug, erythromycin ethylsuccinate, undergoes hydrolysis after administration, releasing the active drug while masking its taste^{24, 30}.

Toxicity: 5-Fluorouracil (5-FU), a widely used anticancer drug, causes severe myelotoxicity when administered directly. Safer prodrugs such as capecitabine, UFT, and S-1 have been developed, which provide similar or better efficacy with reduced toxicity³¹. Polymeric derivatives of 5-FU further enhance controlled release and biocompatibility³².

Weak Pharmacological Activity: Lawsone and its derivatives demonstrate limited potency, but their metal complexes and prodrug forms enhance biological activity³³. Plumbagin, another naphthoquinone, has been converted into prodrugs through chemical modification or metal chelation, improving anticancer activity while reducing toxicity³⁴.

Strategies for Prodrug Formation: Prodrugs can be engineered using a variety of chemical and biotechnological approaches:

Polymeric Prodrugs: Active molecules covalently linked to polymers, offering better stability, site-specific delivery³⁵, and controlled release³⁶.

RSSH-Releasing Prodrugs: Designed to release persulfides, which play roles in redox balance and cytoprotection³⁷.

Phenazine Derivatives (Iodinin, Myxin): Modified into carbonate or carbamate prodrugs to improve solubility and anticancer selectivity³⁸.

Chiral Compound Formation: Use of enzymatic or organometallic catalysis to generate

enantioselective prodrugs of compounds such as lawsone³⁹.

Amine Addition to Sesquiterpene Lactones: Masks reactive groups and improves solubility⁴⁰.

Amino Acid Conjugates: Enhance bioavailability and blood-brain barrier penetration⁴¹.

Single-Chain Lipid Conjugates:

Example: acyclovir lipid derivatives that self-assemble into nanoparticles with extended half-life.

Prodrugs Derived from Various Phytochemicals: Prodrug discovery from natural sources is categorized by the identification, elucidation, derivatization, and chemical modification of secondary metabolites obtained from natural resources, which undergo biotransformation before reaching the binding site and cellular receptors to produce the desired therapeutic effect, overcoming the limitation of the physiological barrier. The role of phytochemicals as potential prodrugs or therapeutic substances against various diseases has come into the spotlight in very recent years. Thankfully, the huge mass of inspiring and capable results of the *in-vitro* activity of many phenolic compounds from plant extracts against several diseases was identified⁴¹. The various natural products used as prodrugs are:

Prodrug of Allicin: Allicin is a sulfur-containing natural compound having several biological properties that are accountable for the characteristic smell and taste of freshly cut or crushed garlic (*Allium sativum*)^{42, 43}. Allicin has anti-microbial, anti-cancerous, and immunomodulatory effects and is used in the treatment of hypercholesterolemia. It is very effective against various health problems, but it has stability issues in the human body.

Allin **Fig. 3B** is a prodrug of allicin **Fig. 3A**, an unstable compound that is transformed into diallyl disulfide. This sulfoxide prodrug is a natural component of fresh garlic that is much more stable

than allicin and is transformed into its bioactive form by the enzyme allinase. This prodrug, after conversion, can act as an anti-bacterial and anti-hyperlipidemic agent⁴².

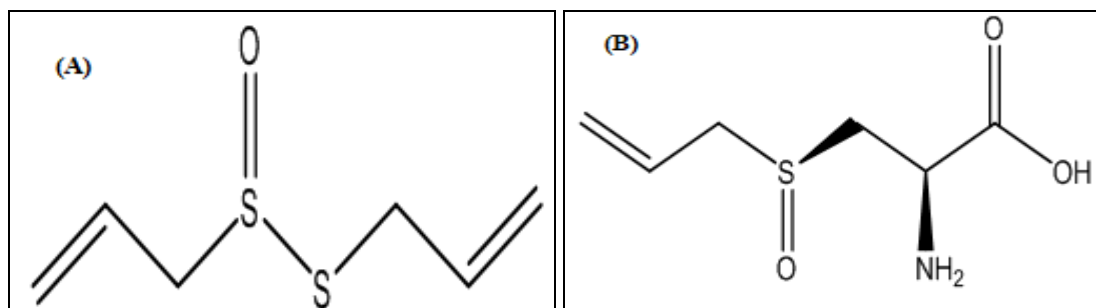


FIG. 3: (A) ALLICIN (B) PRODRUG, ALLIN

Prodrug of Curcumin: Curcumin (diferuloylmethane) is an orange-yellow polyphenolic compound isolated from the rhizomes of turmeric with a varied range of pharmacological effects, like anti-cancerous, antiviral, anti-arthritis, antioxidant, and immunomodulatory effects, but it holds a lot of bioavailability issues^{44, 45}.

The synthesis of curcumin diethyl disuccinate is attained via one-step esterification between curcumin and succinic acid monoethyl ester chloride using 4-(*N,N*-dimethylamino) pyridine as a catalyst⁴⁶. Curcumin diethyl disuccinate, a prodrug of curcumin, has enhanced chemical and metabolic stability; hence, the oral bioavailability is increased, which can lead to the enhanced anti-proliferative activity of the drug. This prodrug is used widely in colon and breast cancer⁴⁷⁻⁴⁹. Curcumin diglutamic acid, an ester prodrug of curcumin, has the potential to be established as an

anti-inflammatory agent due to its enhanced solubility and stability⁵⁰.

Prodrug of Epigallocatechin-3-gallate: Epigallocatechin-3-gallate is the chief catechin found in green tea. It has antioxidant effects, cancer chemoprevention, enhances cardiovascular health, improves weight loss, defends the skin from the damage caused by ionizing radiation, and others⁵¹. The drug has a wide range of effects but has low efficacy. So, the epigallocatechin-3-gallate **Fig. 4A** is converted to a prodrug, proepigallocatechin-3-gallate **Fig. 4B** by acetylation can alleviate mouse laser-induced CNV leakage and reduced CNV area by down-regulating HIF-1 α /VEGF/VEGFR2 pathway and M1-type macrophage/microglia polarization as well as endothelial cell viability, proliferation, migration and tube formation, denoting a novel potential therapy for the age-related macular degeneration⁵².

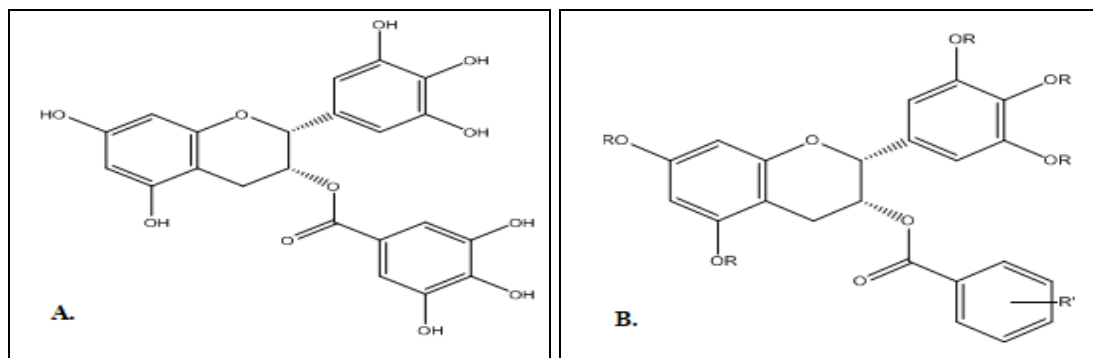


FIG. 4: (A) EPIGALLOCATECHIN-3-GALLATE (B) PRODRUG, PROEPIGALLOCATECHIN-3-GALLATE

Prodrug of Podophyllotoxin: Podophyllin, an ethanolic extract of *Podophyllum peltatum* or *P. emodi*, is a great source of the aryltetralin-type lignan, podophyllotoxin. Podophyllotoxin **Fig.**

5A is a potent anti-cancerous drug, but due to the adverse effects, it is now preferably used in the form of a prodrug. The adverse effects were due to its low water solubility and high toxicity. A

prodrug of podophyllotoxin, 7-hydroxymethyl-2,3-dihydro-1H-cyclopent-a[b] chromene-1-one **Fig. 5B**, is prepared by esterification of the original drug through biotransformation and nucleophilic addition of a sulfhydryl group to the position of the α,β -unsaturated ketone, which produces phenol

anions that promote rapid 1,6-elimination of the intermediate, resulting in the formation of the prodrug. This prodrug is more water-soluble, less toxic, and is considered a promising candidate in cancer therapy^{53, 54}.

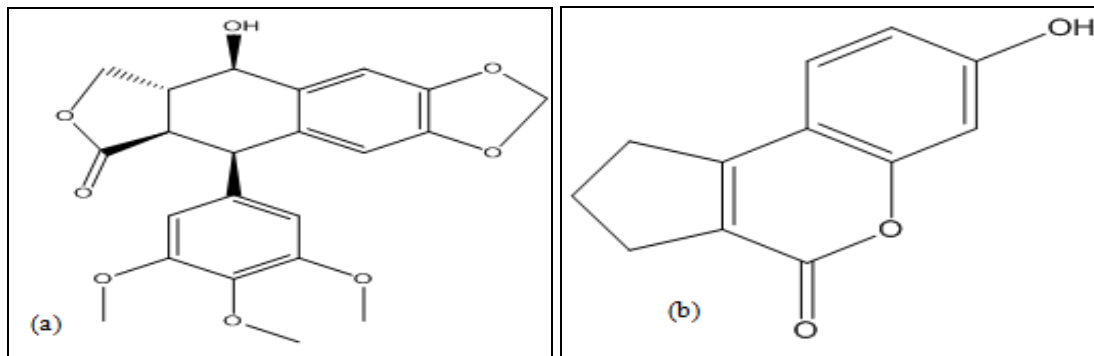


FIG. 5: (A) PODOPHYLLOTOXIN (B) PRODRUG, 7-HYDROXYMETHYL-2,3-DIHYDRO-1H-CYCLOPENT-A[B]CHROMENE-1-ONE

Prodrug of Quercetin and Resveratrol: Quercetin is the chief flavonoid present in various vegetables and fruits. Quercetin possesses a diversity of biological activities, including antioxidant, prevention of oxidation of low-density lipoproteins *in-vitro*, and anticarcinogenic activities. The major drawback of the drug is its bioavailability issues⁵⁵⁻⁵⁸. The esterification of quercetin results in the formation of a prodrug, 3-O-acylquercetins, and quercetin-3-O-palmitate. These prodrugs have effective antioxidant activity and are associated with liposomal membranes. Resveratrol (3, 4', 5-trihydroxystilbene) is a naturally occurring phytoalexin formed by some

spermatophytes, such as grapevines, in response to injury. Resveratrol may provide cardiovascular protection and also possesses anti-inflammatory and anticancer properties⁵⁹. But the compound faces bioavailability issues. The alkylation and structural modification of resveratrol **Fig. 6A** as the 3,5-diglucosyl-resveratrol and piceid **Fig. 6B** and 3-butylated resveratrol inhibit the proliferation and cause death by both apoptosis and necrosis of a human colon carcinoma cell line⁶⁰. The prodrug resveratrol has increased bioavailability due to the improved chemical stability and solubility in water, and hence it is more effective than the original drug^{5, 61}.

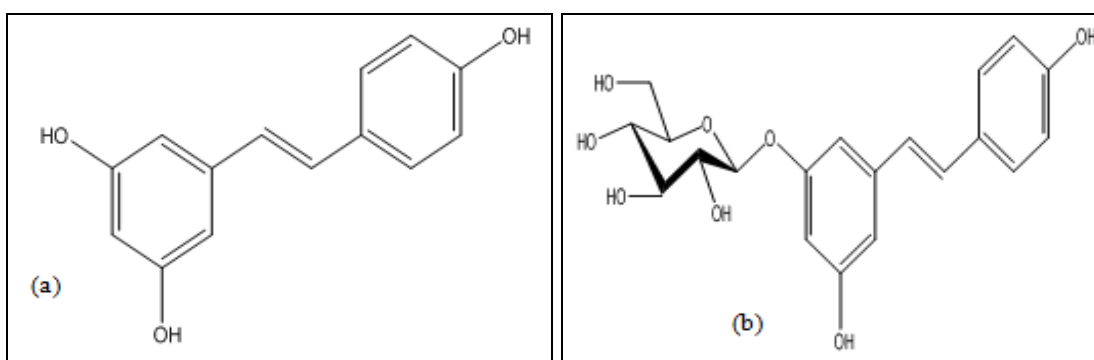


FIG. 6: (A) RESVERATROL (B) PRODRUG, PICEID

Prodrug of Tropoflavin: 7, 8-Dihydroxyflavone (7,8-DHF), also known as tropoflavin, a small flavonoid, is a natural polyphenolic compound found in several vegetables, fruits, and tree leaves. 7, 8-DHF potentially inhibited cancer growth, proliferation, invasion, and metastasis, as

well as various brain-related diseases⁶². Tropoflavin **Fig. 7A** is characterized by poor oral bioavailability and a shorter half-life. A prodrug of tropoflavin named R-13 **Fig. 7B** was synthesized by ester or carbamate group alteration on the catechol ring in the parent moiety, which has

significantly increased oral bioavailability and half-life, which is proven to be more beneficial than the

parent drug. This prodrug is used against various brain-related disorders^{5, 63}.

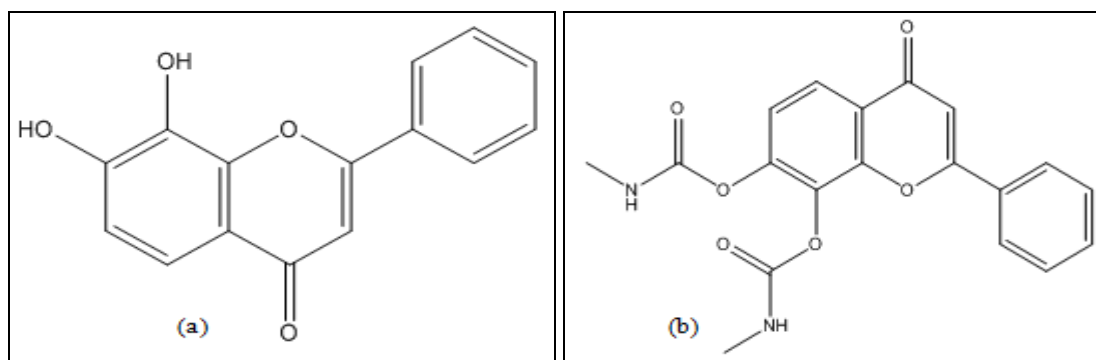


FIG. 7: (A) TROPEFLAVIN (B) PRODRUG, R-13

Prodrug of Baicalein: Baicalein flavonoid, is a hydrophilic drug used as a neuroprotective, anti-depressant, anti-cancerous, antioxidant, anti-inflammatory, and hepatoprotective agent that is incapable of crossing the BBB⁶⁴. A prodrug is formed from the baicalein by various methods, including endogenous transporters (e.g., carrier-mediated prodrug transport), macromolecular delivery mechanisms (e.g., receptor-mediated prodrug transport), and gene-directed enzyme prodrug therapy. This prodrug is more lipophilic due to which allows it can cross the BBB easily & is more effective. This prodrug is used as a neuroprotective and anti-depressant agent^{5, 65, 66}.

Prodrug of Cinnamaldehyde: Trans-Cinnamaldehyde is an aldehydic terpenoid obtained from cinnamon (*Cinnamomum zylanicum*). It is used as an anti-bacterial, carminative, cardiotonic, etc.⁶⁷. Cinnamaldehyde Fig. 8A is a chemically unstable and water-soluble drug that hinders its potential bioactivity. A prodrug formed by the interaction of tryptamine with cinnamaldehyde is known as TRY-CA (Tryptamine-Cinnamaldehyde) Fig. 8B, which is much more chemically stable and much more biologically active than cinnamaldehyde itself. This prodrug is used in the treatment of glioma^{5, 68}.

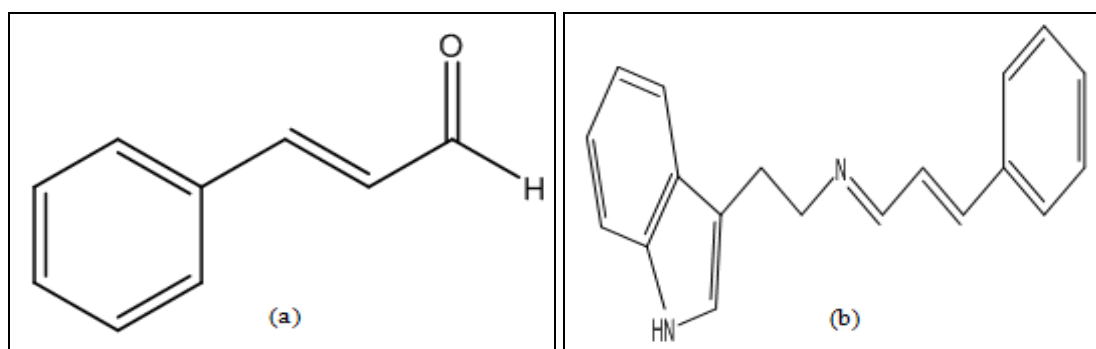


FIG. 8: (A) CINNAMALDEHYDE (B) PRODRUG, TRY-CA

Prodrug of Colchicine: Colchicine is an alkaloid obtained from the extract of Colchicum (*Colchicum autumnale*). Colchicine is being used as an anti-fibrotic, anti-inflammatory, anti-gout agent, etc., but has limited use due to the hepatotoxicity that it produces⁶⁹. Colchicine was hydroxyl-functionalized by substituting the N-acetyl moiety with an N-2-hydroxyacetyl moiety. Afterward, the hydroxyl group was reacted with methoxy PEG-acetic acid to get the hydrolyzable polymeric colchicinoid prodrug. This prodrug has reduced

systemic toxicity, therefore opening the door for its application in cancer therapy and as an anti-viral agent^{70, 71}.

Prodrug of α -methylene- γ -lactone: α -methylene- γ -lactone is a sesquiterpene lactone mostly found in the Compositae family, which has anti-microbial, anti-proliferative, anti-leukemic, and anti-cancerous properties⁷². It has deprived aqueous solubility and a non-selective binding property as a Michael acceptor at undesired targets. A prodrug of

α -methylene- γ -lactone is developed by adding an amine to the parent drug to mask this group from

nucleophiles and enhance solubility, hence getting a more potent drug⁷³.

TABLE 1: SOME NATURAL BIOACTIVE COMPOUNDS AND THEIR PRODRUGS

S. no.	Bioactive compound	Prodrug	Problem overcome	Pharmacological use
1	Allicin	Allin	Increased stability	Anti-bacterial and Anti-hyperlipidemic activity
2	Curcumin	Curcumin diethyl disuccinate	Increased stability and bioavailability	Colon and breast cancer
3	Curcumin	Curcumin diglutamic acid	Improved solubility and stability	Anti-inflammatory agent
4	Epigallocatechin-3-gallate	proepigallocatechin-3-gallate	Increased activity	Age related macular degeneration
5	Podophyllotoxin	7-hydroxymethyl-2,3-dihydro-1H-cyclopent-a[b]chromene-1-one	More water soluble and less toxic	Anti-cancerous agent
6	Quercetin	3-O-acylquercetins and quercetin-3- O-palmitate	Increased bioavailability	Antioxidant effect
7	Resveratrol	3,5-diglucosyl-resveratrol, piceid octanoate and 3-butylated resveratrol	Increased bioavailability, improved chemical stability and solubility in water	Colon cancer
8	7,8-dihydroxyflavone	R-13	Increased oral bioavailability and half life	Various brain related disorders
9	Baicalein	-	More lipophilic and crosses blood brain barrier	Neuroprotective and anti-depressant
10	Cinnamaldehyde	TRY-CA	Chemically stable	Treatment of glioma
11	Colchicine	-	Reduced systemic toxicity	Anti-inflammatory, anti-viral and anti-cancerous
12	α -methylene- γ -lactone	-	Increased solubility	Anti-cancerous agent

CONCLUSION: The prodrug approach offers a versatile and powerful strategy to optimize natural bioactive compounds with limited pharmaceutical applicability. By modifying phytochemicals, researchers can overcome issues such as poor solubility, rapid metabolism, instability, and toxicity. Examples across multiple natural products demonstrate improved bioavailability, better targeting, and reduced adverse effects.

Future directions in prodrug research include the design of intelligent linkers and spacers, polymeric and nanocarrier-based systems, and the integration of computational modeling to predict activation and optimize pharmacokinetics. Given their potential, natural product-derived prodrugs will likely remain central in drug discovery and development.

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